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To	Ganapathy Krishnan	**Pages**	5
Company	United states Patent and Trademark Office	**Date**	03 July 2009
Fax	001 571-273-8300		
From	Gary Evans		

Research Innovation Services - Technology Transfer
The Sir Colin Campbell Building
University of Nottingham
Innovation Park (UNIP)
Triumph Road
Nottingham, UK
NG7 2TU

Direct line 44 (0) 115 8467890 **E-mail** gary.evans@nottingham.ac.uk

Fax : 44 (0) 115 82 32181

Subject **US Application No 10/549,384**

Dear Krishnan

Please find attached a copy of our request to discuss certain issues regarding your report on the final rejection of this patent application which the inventors wish to discuss with you on the 7th July 2009. I have also attached a copy of the paper Kispal et al. (1987). Which is relevant to our discussion of your comments.

Please acknowledge receipt of this communication either by fax or by e-mail (gary.evans@nottingham.ac.uk)

Best regards,

Dr Gary Evans
Head of intellectual Property Management
RIS
University of Nottingham
Nottingham
England
United Kingdom

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Response to USPTO Final Rejection Report **3 July 2009**

Application number 10/549,384; Filing date 11/03/2005;

First named inventor Paul Leonard Greenhaff,

Attorney docket number SWIN 3306 , confirmation no 5375 , Art Unit 1623

Examiner **Krishnan, Ganapathy**

Report mailing date : 27 April 2009

Date report received by Applicants/Inventors: **17th June 2009**.

We apologise for not responding sooner but as you can see from the dates above your report has taken several months before it was sent by our patent agents.

Request for telephone discussion with examiner

We have recently received your final rejection report and we would welcome an opportunity to discuss the prior art and your conclusions because we do not know if there is a misunderstanding on the teachings of the prior art or if the claim drafting is the reason for our invention being regarded as anticipated and obvious. The inventors are recognised experts in this field and the subject matter of the invention was not regarded as the state of the art when they first disclosed their invention.

In order to facilitate our discussions we have endeavoured to set out below a response to the issued raised in your report.

1) Novelty - Anticipation

a. Rejection of claim 58 for recitation of the term "carnitine substance" as being indefinite. The applicants are willing to amend the term to L-carnitine so that it is definite.
b. Rejection of claim 65 for recitation of the term "simple" the applicants are willing to delete the term "simple" or delete claims 64,65, 66 and 67 and related claims".
c. *The rejections of Claims 58-63, 76-80 and 91-92 as being anticipated by Davies,*
d. *The rejections of Claims 58-65, 74,76-83 91and 93-102 as being anticipated by Pola,*
e. *The rejections of Claims 93-103, as being anticipated by Bohles*

All based on the compositions which were previously disclosed:-

Davis disclosed that the composition of carnitine and glycine or arginine (both amino acids) enhance the intestinal absorption of both carnitine and glycine by formation of a complex between the two molecules. However, this does not disclose a mechanism by which the uptake and retention of carnitine in skeletal muscle is increased. Importantly, increasing glycine or arginine concentration will have no effect on the insulin concentration in the intestinal lumen because it is not present here. However, even if it was, Davis teaches of a carnitine/glycine or arginine complex (i.e. a new chemical entity) that could very well be metabolically inert. The novelty of our application focuses on increasing blood insulin to promote muscle carnitine uptake. This could not occur in the intestine nor was this mechanism even tangentially alluded to in the work of Davis. Indeed, Fig. 3 in our filing shows plasma carnitine to be lower in the presence of carbohydrate, which would not be the case if carbohydrate was promoting intestinal absorption of carnitine.

presence of carbohydrate, which would not be the case if carbohydrate was promoting intestinal absorption of carnitine.

Pola discloses a series of compositions, consisting of a combination of various forms of L-carnitine and ribose or amino acids or monosaccharides, which apparently was capable of protecting ATP content in papillary (heart) muscle under anoxic condition (i.e. no oxygen), i.e. extremely stressful conditions. However, Pola at no point alludes to insulin, nor its effect on carnitine uptake. Indeed, carnitine retention has not been determined. Furthermore, none of the various compositions cited by Pola contain sufficient quantities to have any measurable effect on plasma insulin concentration, and certainly will not augment tissue carnitine content above that seen with carnitine alone. As our filing describes, L-carnitine administration per se (in quantities far exceeding those described by Pola) has no effect on muscle carnitine content (Fig 10), which in itself is a different response to that seen in heart, and furthermore, insulin needed to be increased to above ~50 mU/l for any increase in muscle carnitine retention to be observed (Fig. 6), which is far, far in excess of anything that the compositions described by Pola could achieve.

Bohles discloses the use of intravenously administered carnitine and affects on metabolism, but no evidence is presented for carnitine uptake and retention in skeletal muscle, and the changes in insulin concentration were statistically no different between periods I-III (see Table II). Furthermore, irrespective of this point, the central premise of Bohles is that increasing lipid and decreasing carbohydrate availability appears to mediate a metabolic effect – this is the opposite of what we have proposed and therefore does not detract from the novelty of our filing. Bohles disclosures cannot therefore have been regarded as anticipating our invention.

Our composition does not claim to increase the intestinal absorption of carnitine, but the uptake of carnitine into skeletal muscle from systemic circulation by an insulin dependent mechanism. This will obviously require the simultaneous elevation of carnitine and insulin in blood, and the latter is achieved by contemporaneously administered carbohydrate, protein or amino acids. We would suggest the amendment of the existing claims to distinguish this from those disclosed and anticipated by the prior art.

Obviousness

The examiner writes
Davis teaches compositions comprising carnitine and glycine, which is useful for carnitine absorption (glycine, an amino acid: the agent to increase insulin concentration as in instant claims 58 and 63; pages 5-6; Examples 1-7; limitations of claims 58-63;page 3, lines 16-21). Davis discloses the said composition in the form of an aqueous solution (page 3, lines 48-50).

There is no suggestion in Davis that glycine alters insulin levels, or that intestinal absorption of carnitine would be affected if it did. It is important to note that insulin is not present in the lumen of the intestine nor has insulin been implicated in intestinal absorption of carnitine. Indeed Davis attributes the increased intestinal absorption to the formation of a new chemical entity from glycine or arginine and carnitine.

Gross teaches the uptake and retention of carnitine by rats (abstract, page 266, right column, section entitled-Intestinal levels of carnitine trough page 267). The study also deals with sodium dependent uptake. Gross may not have specifically taught carnitine retention in skeletal muscle. But his teaching still deals with carnitine retention in body tissue.

Gross also only deals with intestinal absorption of carnitine; there is no information relating to uptake or retention of carnitine in skeletal muscle. There is no experimentation concerning the

effect of insulin on carnitine uptake. Gross does however refer to the work of Kispal et al. (1987) in the Discussion, pertaining to the effect of insulin on carnitine uptake in perfused liver (paper attached). However, the work of Kispal et al. (1987) shows that insulin had no effect on liver carnitine transport in fed animals and reduced uptake in fasted animals. This is the opposite of what we describe in our application. Gross therefore does not teach of increasing carnitine retention in body tissues, but in intestinal absorption and even then not in relation to insulin.

Bohles teaches a method increasing carnitine retention by administration of amino acids, glucose (both insulin increasing agents) and L-carnitine to piglets (page 9, abstract and right column, see under Experimental Design). The administration is seen to produce increased energy gain and improvement in nitrogen balance, all of which indicate carnitine retention. Applicants argue that that administration of carnitine with glucose shows a decrease in insulin levels as shown in Table II, period 3 (page 11). According to Bohles (page 9, Experimental Design) during period 3 part of glucose was substituted with fat. During period 1 only glucose was fed. In Table II it can be seen that during period 1, when only glucose was fed insulin level is high. During period 3 the insulin level is low which is to be expected since the amount of glucose intake has been reduced. So, as long as glucose is intake is there it is going to increase the insulin level and also help with the retention of carnitine.

If the amount of glucose is reduced, which as the examiner points out will lower the insulin concentration, how can it be obvious that insulin will stimulate carnitine retention? Surely, it suggests the opposite (i.e. a decrease in insulin concentration (or as Bohles suggests an increase in fat availability) promotes carnitine retention. Irrespective of this point, Bohles showed that there was no statistical difference between the insulin levels in each of the three study periods and therefore any interpretation of the effect on carnitine retention is not attributable to insulin. Indeed, the changes in carnitine levels were attributed to regulatory activities of the kidney. There is no information from Bohles on the retention of carnitine in skeletal muscle.

Pola teaches a food/dietary supplement comprising L-carnitine and acyl derivatives of L-carnitine and Ribose (a simple sugar; pages 6-9; pages 11-14; limitations of claims 58-65, 76-83). The composition can be in the form of syrup (page 12, line 3; limitations of claims 74, and 91). Pola teaches that his composition is an effective supplement for prevention of skeletal muscle dysfunction (page 2, second full paragraph) and for energy supply during prolonged physical activity and muscle fatigue. In order for carnitine to perform this function it must be absorbed and retained in the skeletal muscle. Even though ribose may not be taught to increase insulin levels
Davis teaches the use of glycine, an amino acid (as instantly claimed) for carnitine absorption and Bohles teaches (and has also demonstrated as explained above) the use of glucose, which increases insulin level. Hence, one of ordinary skill in the art based on the teaching of Bohles and Pola would use a composition comprising carnitine and a carbohydrate like glucose that increases insulin level, in a method to increase carnitine retention. This is suggested mainly by the teachings of Boles and Pola. The instant claims are rendered obvious bythe prior art.

Pola teaches of compositions capable of protecting ATP content in heart, not skeletal, muscle and under conditions of extreme physiological stress. At no point is there reference to insulin, nor its effect on carnitine uptake. Indeed, carnitine retention was not determined. Additionally, none of the various compositions cited by Pola contain sufficient quantities of ingredients to have any measurable effect on plasma insulin concentration, and will not augment skeletal muscle carnitine content. Davis only teaches effect on intestinal absorption, and does not disclose a mechanism by which the uptake and retention of carnitine in skeletal muscle is increased by insulin. Indeed, insulin is not present in the lumen of the intestine and Davis attributes the increased absorption from the intestinal lumen to the formation of a new chemical entity from glycine or arginine and carnitine. Bohles shows no statistical effect on insulin levels by glucose in his study, but even if they were statistically different the central premise of Bohles is that increasing lipid and decreasing glucose availability appears to

mediate a metabolic effect – this is the opposite of what we have proposed. There is no suggestion in any of the prior art that contemporaneously administration of an agent which increased insulin in the systemic circulation would provide for uptake of carnitine by skeletal muscle
We enclose a copy of Kispal et al. (1987).

We request that the examiner reconsiders his decision and welcome the opportunity to discuss the issues with the examiner on the 7th July 2009.